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Neoplastic and Potentially Preneoplastic Changes in the Upper Respiratory Tract of Rats and Mice

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The National Toxicology Program (NTP) database was examined for tumor incidences and chemicals producing tumors in the nasal cavity, larynx, or trachea. Slides from appropriate studies were then examined in an attempt to unify terminology and make comparisons between induced and spontaneous tumors and hyperplastic or preneoplastic lesions produced in the upper respiratory system. An attempt was also made to compare the species affected, route of administration, and tumor types produced by different chemicals. The results are not meant to be all inclusive of the NTP database but to be representative of observed trends. General conclusions that emerged from this review were that rats are much more susceptible to epithelial tumors of the nasal cavity than mice; that only mice have been reported to have chemically induced hemangiomas and hemangiosarcomas of the nasal cavity; that tumors of the olfactory epithelium and squamous cell tumors of the respiratory epithelium are almost uniformly malignant and invasive, while other tumors of the respiratory epithelium are typically less invasive; that most chemically induced tumors of the olfactory region, either mesenchymal or epithelial, do not require an inhalation route of exposure but appear to occur by systemic targeting of this region; and that a uniform nomenclature for tumors of the nasal cavity is needed.

Introduction

The initial problem for the experimental pathologist in evaluating neoplasia in the upper respiratory tract and, in particular, the nasal cavity, is the selection of a widely acceptable tumor classification system. The choice largely depends on the pathologist's personal experience and on the personal biases that develop as the full range of lesions unfolds. This dilemma was highlighted by Harold L. Stewart in his preface to *Nasal Tumors in Animals and Man*, edited by Reznik and Stinson (*1*). A portion of Stewart's comments are as follows:

> . . . tumors in animals may differ in appearance and behavior from tumors of corresponding sites in humans. The exact definitions of the tumors induced in rodents and their histologic typing still await further study for the development of a proper classification and nomenclature. This could be accomplished if . . . several pathologists knowledgeable about tumors of the nasal passages in rodents. . . come together with their respective pathologic material and records and carefully work out an acceptable classification.

It would be highly desirable for such a panel of pathologists to convene and establish a uniform classification system for the nose, as was suggested by Stewart 7 years ago. The classification primarily used in this presentation (Table 1) was only intended as a guideline that seemed to correlate with the majority of chemically induced lesions observed in the National Toxicology Program (NTP) Archives. The terminology is, for the most part, a combination of terms taken from the work of Feron et al. (*2*), or from the human classifications published by Heffner (*3*) and Michaels (*4*). As a bench pathologist, my purpose in this presentation was to comment on the choices of morphologic descriptors that might be useful in locating lesions in the upper respiratory tract; give some information from the NTP database as to the spontaneous incidence of tumors in the upper respiratory tract; highlight the chemically induced neoplastic lesions in the upper respiratory tract; make comparisons as to tumor type, route of exposure, and species affected between chemicals; and briefly comment on which nonneoplastic lesions should be diagnosed as possibly pertaining to the development of neoplastic lesions.

Topography

In terms of choices of topographic descriptors in the nose, neoplastic lesions should be located in one of four or five general sites, which seem to biochemically represent distinct sites of chemical interaction. Proceeding from anterior to posterior, these sites are: the region of squamous epithelium (nares, vestibule, ventral meatus and incisive duct), the region of single or stratified cuboidal or transitional epithelium (anterior lateral wall and the anterior tips and lateral surfaces of the maxillary

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Table 1. Provisional outline for classification of lesions in the upper respiratory tract of rats and mice.

- Tumors of squamous epithelium
- Tumors of respiratory epithelial region
  - Squamous cell carcinoma
    - Focal
    - Diffuse (verrucous)
    - Adenosquamous
  - Squamous cell papilloma
  - Papillary or pseudoglandular adenoma
    - Respiratory epithelial differentiation
    - Epidermoid transitional differentiation
  - Papillary or pseudoglandular carcinoma
    - Respiratory epithelial differentiation
    - Epidermoid transitional or cylindric cell differentiation
  - Adenomas and carcinomas of submucosal glands
  - Carcinoma of the glands of the maxillary sinus
- Tumors of the olfactory epithelial region
  - Neuroepithelial carcinoma
    - Sustentacular cell differentiation (Flexner-Wintersteiner, Homer Wright, vascular rosettes)
    - Basal cell differentiation or neuroblastoma-like rosettes (Flexner-Wintersteiner or Homer Wright rosettes)
    - Solid (carcinomatous) pattern
    - Neuroendocrine differentiation
    - Mixed
    - Undifferentiated
  - Bowman's gland carcinoma
  - Adenosquamous carcinoma
  - Squamous cell carcinoma
  - Epidermoid (inverted) papilloma
- Mesenchymal tumors
  - Rhabdomyoma/rhabdomyosarcoma
  - Mixed epithelial/mesenchymal tumor (collision tumor rhabdomyosarcoma/neuroepithelial carcinoma)
  - Hemangioma
  - Hemangiosarcoma
  - Chondroma
  - Chondrosarcoma
  - Osteoma
  - Osteosarcoma
  - Fibroma
  - Fibrosarcoma (sarcoma, NOS)
  - Oncocytoma
  - Malignant Schwannoma
  - Fibrous meningioma
- Nasolacrimal duct tumors
  - Squamous cell papilloma
  - Squamous cell carcinoma
- Poorly differentiated spindle-cell tumor of dental or nasolacrimal duct origin
- Potentially/preneoplastic esions
  - Squamous metaplasia
  - Dysplasia of squamous epithelium
  - Keratin plugging
  - Respiratory basal cell hyperplasia
  - Olfactory epidermoid basal cell hyperplasia
  - Olfactory basal cell hyperplasia
  - Hyperplasia/atypia of Bowman's glands

and nasal turbinates), the respiratory epithelial region, the olfactory epithelial region, and possibly the nasopharynx.

Tumors of mucosal glands should be identified as separate entities from surface epithelial tumors, if possible, and placed in the appropriate region. Tumors of the maxillary sinus glands should be identified as separate entities, as should the tumors of the nasolacrimal ducts or of other site-specific structures such as the vomeronasal organ. Tumors of the larynx and trachea should be separated, based on the epithelium of origin (squamous or respiratory), and tumors of mucosal glands should be separated from surface epithelial tumors.

Tumor Incidence

The incidence of spontaneous tumors of the upper respiratory tract in the NTP Archives was far less than 0.5% for any tumor type in any location. Apparently the most common nonlymphoid spontaneous tumor seen in the upper respiratory tract of rats was a squamous cell neoplasm. These tumors when present, must be discriminated from metastatic tumors arising in the oral cavity, skin, or from the Zymbal gland. A spontaneous tumor, apparently arising from the periodontal ligament and sometimes extending into the nasal cavity, has also been described by Cullen et al. (*5*). Spontaneous tumor incidences for the upper respiratory system of F344 rats and B6C3F$_1$ within the NTP database as of May 1988 were as follows in Table 2.

A few general observations concerning the database as it relates to chemically induced tumors might bear mentioning here. First, rats were, in general, more susceptible to tumor formation in the upper respiratory tract than mice. Second, when tumors occurred in the respiratory region of the nose, they occurred most frequently on the nasal and maxillary turbinates and in the dorsal and ventral lateral wall recesses. Third, olfactory epithelial tumors were generally malignant, whereas respiratory or transitional epithelial tumors were of much lower malignant potential or benign. Fourth, vascular tumors of the nasal cavity were diagnosed exclusively in mice and not rats, and finally, mixed morphologies within tumors and foci of squamous metaplasia overlying papillary projections frequently were seen.

Chemically induced lesions from the NTP Archives will be presented proceeding from the anterior regions caudally.

Tumors of Squamous Epithelium

Tumors from the region of squamous epithelium of the nares and nasal vestibule were apparently rare. When present, classic squamous cell carcinomas and papillomas occurred and sometimes formed vegatative or erosive lesions extending from the nasal orifices or onto the external nasal tissue, sometimes leading to their classification as skin tumors instead of primary nasal tumors (Table 3).

Tumors of Respiratory and Transitional Epithelium

The respiratory and transitional regions of the nasal cavity were the most common sites for the occurrence of squamous cell tumors. Squamous cell carcinomas

Table 2. Incidence of spontaneous neoplasia in upper respiratory tract of F344 rats and B6C3F$_1$ mice.

	Male mice	Female mice	Male rats	Female rats
Corn oil gavage controls				
Squamous cell carcinoma	0/2091	0/2093	2/2099	0/2100
Squamous cell papilloma	0/2091	0/2093	1/2099	0/2100
Adenoma, respiratory epithelium (all types)	0/2091	0/2093	2/2093	0/2100
Untreated controls				
Squamous cell carcinoma	0/1692	0/1689	1/1596	0/1643
Papilloma, NOS	0/1692	0/1689	0/1596	0/1643
Trachea				
Tracheal gland adenocarcinoma	0/1692	0/1689	1/1540	0/1597

occurred more frequently than squamous cell papillomas, and three possible subtypes were seen in the experimentally induced tumors examined: focal, diffuse, and adenosquamous. Focal squamous cell tumors occurred with local invasion and extensive lymphatic extension within the mucosa of the nasal cavity. A diffuse type of squamous cell carcinoma was also frequently seen that appeared to involve the entire nasal cavity unilaterally with obscurement of the nasal and maxillary turbinates (Plate 1). This tumor was particularly commonly seen with 1,4-dioxane, a chemical that was administered in the drinking water to Sprague-Dawley rats. The growth pattern of this tumor was characterized by diffuse scalloped margins, failure of cells to mature, parakeratotic hyperkeratosis, and a lobular extension through the maxillary bone to the subcutis of the overlying skin. Adenosquamous carcinomas were rarely seen but when present, extended into the olfactory region from the dorsal lateral wall, forming both glands of mucous-secreting or cuboidal cells as well as typical squamous epithelial pearls (Plate 2).

Tumors arising from respiratory epithelium frequently formed papillary masses, extending into the lumen of the nasal cavity, or pseudoglandular structures, formed by tubular outgrowths or downgrowths of surface epithelium (Plate 3*A*, *B*, *C*). When crowded columnar epithelium predominated with a relatively low mitotic rate and little evidence of stratification of nuclei, proliferation of basal cells, or local invasion, these tumors were referred to as papillary or pseudoglandular adenomas of respiratory epithelium.

Tumors arising from the lateral wall sometimes had features typical of the pseudostratified cuboidal epithelium seen in this location. These tumors often grew along the surface of the lateral wall, became solid and squamoid in appearance, and had little if any tendency for invasion into the lamina propria. Protein-filled spaces and perivascular lymphatic lakes often further characterized these tumors (Plate 4*A*,*B*). Because of the squamoid appearance of these tumors they were termed "epidermoid" adenomas of respiratory epithelium, but the term "transitional cell adenoma" might be more appropriate if that term is used to describe the corresponding normal epithelium of the anterior lateral wall.

Many tumors of the turbinates were complicated by mixed features of both respiratory and stratified cuboidal epithelium. This feature was further complicated on occasion by focal squamous metaplasia.

Carcinomas of the respiratory epithelium also had varying morphologies with two types appearing most frequently. The most frequent malignant tumor type, by far, was a papillary, tubular, or pseudoglandular pattern that had stratification of nuclei, prominent mitotic rate, anisonucleosis, and hyperchromatic nuclei or nuclei with unusual chromatin patterns and apparent basal cell proliferation. Since these tumors are relatively slow growing, and a degree of extension into the lamina propria is common for all papillary tumors, whether benign or malignant, some tumors were diagnosed as being of low malignancy, based on the cytologic evidence alone. A few tumors showed a resemblance to colonic adenocarcinomas, which has been described for some malignant sinonasal tumors in man that are suspected of being environmental induced (*3*). The proximity of the observed tumors to the olfactory epithelium also indicates their possible origin from the olfactory mucosa. They were classified simply as papillary or pseudoglandular carcinomas with respiratory epithelial differentiation.

The other main malignant tumor type formed from surface epithelium was associated with the lateral wall and the maxillary or nasal turbinates. This tumor consisted of exophytic and endophytic tubular infoldings of respiratory epithelium with abundant basal cell proliferation, that seemed to form a progression from respiratory epithelium, to a "cylindric cell" pattern, to solid tubules of "epithelioid" cells that invaded the lateral wall. Such tumors sometimes invaded adjacent soft tissue or the periodontal ligament of the incisor tooth root

Table 3. Chemicals in the NTP archives that induced squamous cell carcinomas in the anterior nasal cavity.

Chemical	Species affected	Route
1,2-Dibromo-3-chloropropane	F344 rat	Inhalation
	B6C3F$_1$ mouse	Inhalation
1,2-Dibromoethane	F344 rat	Inhalation
α-Epichlorhydrin	SD rat	Inhalation
Dimethylcarbamyl chloride	SD rat	Inhalation
Hydrogen chloride/ paraformaldehyde	SD rat	Inhalation
Dimethylvinyl chloride	OM rat	Drinking water

(Plate 5*A*,*B*). This tumor was classified as a papillary or pseudoglandular carcinoma with "epidermoid" differentiation. The same tumor apparently has also been called "transitional cell carcinoma" or "carcinoma of the cuboidal epithelium of the lateral wall."

The remaining malignant tumors that were seen were observed only once for each of the following examples. The first was a solid downgrowth of basallike, slightly elongated cells from the anterior lateral wall. The cells were hyperchromatic, had a high mitotic rate, scant cytoplasm, and appeared to be invading the lateral wall. The last type of malignant tumor observed in the respiratory epithelial region was of uncertain etiology but was found invading the maxillary sinus, periodontal ligament, region of the nasolacrimal duct, and extending around nerve sheaths and into the masseter muscle. Morphologically it consisted of well-differentiated glandlike structures lined with ciliated epithelium (Table 4).

Tumors of Mucosal Glands

Mucosal gland tumors occurred much more rarely in the NTP Archive material than tumors of the surface epithelium. The more common type seen consisted of narrow ductlike structures in the lamina propria, usually on the septum, and frequently near the vomeronasal organ (Plate 6*A*,*B*). Mitotic figures were fairly numerous, but abnormal mitotic figures were rare. Occasionally the ductular epithelial structures were clearly invading nerve sheaths or were associated with the destruction of the nasal septum. Ductular structures frequently tapered into narrow ribbons or small islands of cells. Rarely highly malignant and invasive spindle cell tumors appeared to arise from such tubular structures. The origin of the ductular structures appeared to be the mucosal gland ducts.

A second type of glandular tumor was very rare and consisted of well-differentiated serous glands loosely aggregating into a mass compressing and elevating the overlying mucosa (Plate 7). The primary features of neoplasia included anisonucleosis; hyperchromatic or vesicular nuclei, and abnormal organization into ribbons of small, slightly hyperchromatic glands. Mitotic figures were rare, but the compression of adjacent glands and elevation of the overlying epithelium was clear. The few tumors of this type observed were considered to be adenomas.

Tumors of the glands of the maxillary sinus were observed rarely in the NTP Archive material, and when present, such tumors had not been considered to be compound induced. In all cases these tumors invaded around the periodontal ligament of the incisor tooth root (Plate 8*A*,*B*). Tumor morphology was characterized by serous glands with acini less organized and smaller than the normal maxillary sinus glands. Nuclei were hyperchromatic, and the mitotic index was moderately high. In some sections the only indication of the presence of a neoplasm was proliferation of small atypical acini in the ligament, a feature easily overlooked (Plate 8*C*). All of the tumors observed were diagnosed as carcinomas based on invasion of the periodontal ligament. Because the alveolar bone of the incisor tooth is incomplete, some of the observed invasion may actually be an extension of the tumor between the alveolar bone plates. Nevertheless, all of these tumors should be considered to be malignant, due to extensive periodontal destruction, until further characterization proves otherwise.

Table 4. Chemicals in the NTP Archives inducing papillary adenomas and/or carcinomas of the respiratory or transitional epithelium.

Chemical	Species affected	Route
1,2-Dibromo-3-chloropropane	F344 rat, B6C3F$_1$ mouse	Inhalation
1,2-Dibromoethane	F344 rat, B6C3F$_1$ mouse (female)	Inhalation
1,2-Epoxybutane	F344 rat	Inhalation
Propylene oxide	F344 rat	Inhalation
Dimethylvinyl chloride	F344 rat	Gavage
2,6-Xylidine	F344 rat	Feed
2,3-Dibromo-1-propanol	F344 rat	Skin painting
Nitrosaminoketone (NNK)	F344 rat	Intraperitoneal

Tumors of Olfactory Epithelium and Bowman's Glands

Tumors of the olfactory epithelium will be grouped under the common term "neuroepithelial carcinoma." The idea of grouping all tumors of this epithelium under neuroepithelioma was first proposed by Rivenson (*6*) and further elaborated by Feron et al. (*2*). The main objection to the use of the term "neuroepithelioma" is that the term may suggest benign tumors to some; this group of neoplasms most certainly is not. The other objection is that the term "neuroepithelioma" strongly suggests the neural features of the tumors (neuroblastoma, esthesioneuroepithelioma) but does not conjure up the epithelial or carcinomatous features commonly observed. The modifiers to define subtypes under this classification have been presented by Feron et al. (*2*) and this system will be used with some modifications. There were six main types of olfactory epithelial tumors in the NTP database (Tables 1 and).

Tumors with features of sustentacular cells are common in the olfactory region. Both solid masses and glandlike structures or rosettes are formed. When present, rosettes are of the Flexner-Wintersteiner type or are pseudo or vascular rosettes. Cellular characteristics suggestive of sustentacular cells include basally located, often vacuolated cytoplasmic processes, centrally or slightly peripherally located nuclei with somewhat of a marginated chromatin pattern, and a short apical segment that marginates an open space producing glandlike structures. Several transmission electron micrographic studies have demonstrated these cells to have secretory

vesicles, surface modifications, and other structures compatible with their identification as sustentacular cells (*1,2*).

A second olfactory tumor type is composed of small basophilic cells with hyperchromatic nuclei and prominent nucleoli and with a large nuclear-to-cytoplasmic ratio. These cells often seem to form intraepithelial clusters within the olfactory epithelium and to grow downward intermittently in linear bands from the epithelial surface. Rosettes also are formed by these cells, usually of the Flexner-Wintersteiner or Homer Wright type. These tumors frequently invade through the cribiform plate into the brain, and they have features characteristic of neuroblastomas (Plate 10*A,B*). Unlike human neuroblastomas, these tumors have little in the way of eosinophilic fibrillar neural stroma in the nasal cavity. The tendency for these cells to form dense bands and sheets beneath and within the epithelium and their undifferentiated appearance has led to their classification as basal cells by some authors and neuroblastomas by others.

A third pattern observed apparently forms as a result of confluent growth of endophytically proliferating surface epithelium, forming sheets of cells with large nuclei, marginated chromatin, and single prominent nucleoli. This growth pattern, suggestive of a solid epithelial sheet with no other features, is termed the solid or carcinomatous pattern. Invasion through the cribiform plate into the meninges was also seen with this pattern.

No examples of neuroendocrine differentiation were found in the sections examined in this review, although some solid tumors were stained by the Sevier-Munger method in an effort to demonstrate neuroendocrine granules; none were demonstrated. Immunohistochemical staining for neuron specific enolase was also negative.

Probably one of the more common olfactory tumor patterns seen in the NTP Archives was a mixed pattern containing features of several of the above types.

Rarely an undifferentiated tumor was seen that was markedly anaplastic and bore little resemblance to any of the above olfactory epithelial tumor types. Frequently these tumors had both a sarcomatous and epithelial appearance with cells being quite large and pleomorphic, having variable but sometimes abundant fibrillar eosinophilic cytoplasm and large vesicular nuclei with marginated chromatin and a very prominent nucleolus (Plate 11). Although these tumors have been classified as undifferentiated carcinomas or carcinosarcomas, they bear more similarities to rhabdomyosarcomas and will be discussed under mesenchymal tumors.

Bowman's gland tumors were frequently seen with chemicals causing tumors in the olfactory region. These tumors appeared to arise within a background of diffuse Bowman's gland hyperplasia, hypertrophy, atypia, and necrosis. Early tumors formed multifocally as solid aggregates or clumps of larger more atypical cells within the generalized proliferation (Plate 12). Invasion throughout the lamina propria and through the cribiform plate seemed to follow. Possibly, such tumors are the precursors of the solid carcinomas described above, but both nuclear and cytoplasmic differences (Bowman's gland tumors had larger nuclei, more uniform distribution of chromatin, and more basophilic cytoplasm) seemed to be present (Plate 13).

Adenosquamous carcinomas arose in the olfactory region, apparently from Bowman's glands or from downgrowths into Bowman's glands. Such tumors grew into the nasal or frontal bones or penetrated the cribiform plate. Features are as previously described.

Squamous cell carcinomas were observed in the olfactory region, and some appeared to arise in the ethmoid recesses or along the septum. Large or extensively invasive tumors may have arisen more anteriorly in the respiratory epithelial region and extended into the olfactory region. Growth through the maxillary bone was not uncommon.

Downgrowths of epithelioid or squamoid epithelium, apparently from the basal epithelial region of the olfactory mucosa into the lamina propria were seen, particularly following NNK administration (Plate 14). These downgrowths somewhat resembled inverted papillomas as described in man. Margins seemed to be well defined within basement membranes and to appear as lobulations or islands beneath and were connected to the surface. Although the initial impression in viewing this epithelium was that of squamous metaplasia, such areas lacked squamous maturation zones, and cells tended to be more cuboidal and to lie more perpendicular than parallel to the basement membrane. Parakeratotic cysts were also seen. Although the origin and nature of these structures is not clear, they seemed to be slow growing, have a very low malignant potential, or to be benign. Structures of this type were frequently seen trapped within malignant olfactory tumors, apparently overgrown by the more malignant epithelium.

Table 5. Chemicals causing tumors of the olfactory epithelium or Bowman's glands.[a]

Chemical	Species affected	Route
Tris(aziridinyl)-phosphine sulfide	F344 rat	Intraperitoneal
Nitrosaminoketone (NNK)	F344 rat	Intraperitoneal
Procarbazine	F344 rat/B6C3F$_1$ mouse	Intraperitoneal
p-Cresidine	F344 rat	Dietary
2,6-Xylidine	F344 rat	Dietary
Dimethylvinyl chloride	F344 rat	Oral gavage
Bis(chloromethyl)-ether	F344 rat	Inhalation and parenteral

[a]Note that most chemicals appearing on this list were not administered by inhalation, but they appear to act via specifically targeting the nasal cavity and the olfactory epithelium in particular.

Mesenchymal Tumors

Mesenchymal tumors in the nasal cavity were far more prevalent in the olfactory than in the respiratory region. The chemicals listed in Table 6 were not administered by the inhalation route and induced nasal rhabdomyomas and rhabdomyosarcomas in rats.

Rhabdomyosarcomas, rhabdomyomas, and mixed epithelial and mesenchymal tumors, and possibly some undifferentiated sarcomas were the only chemically induced mesenchymal tumors induced in the nasal cavity of rats in the NTP Archives. Nasal hemangiosarcomas and hemangiomas were found exclusively in mice, and they were the only mesenchymal tumor in the nasal cavity of mice clearly associated with compound administration. The other mesenchymal tumors of the nasal cavity that will be described below appear to be spontaneous or of such a low incidence as to make association with treatment difficult.

Rhabdomyomas and rhabdomyosarcomas diagnosed in the nasal cavity are intriguing since the cell of origin is not present as a mature tissue in this location. Supposedly, an as yet unidentified mesenchymal cell in the lamina propria undergoes malignant transformation and expresses the striated muscle phenotype. Examples taken from the NTP Archives had features of well-differentiated striated muscle as well as more primitive, rounded cells of various sizes with various nuclear morphologies. One cell that was seen, that is perhaps the most primitive precursor cell, was a rounded cell with a condensed nucleus and scant cytoplasm, slightly larger than a lymphocyte. These cells were seen in areas of tumor growth, along with larger cells with more abundant, fibrillar eosinophilic cytoplasm that became progressively more elongate and syncytial (Plate 15). Nuclei, whether single or multiple, had a uniform, pale staining or very hyperchromatic chromatin pattern, usually they were situated in or near the center of the cell. Rows of nuclei were occasionally observed. Although discrete tumor masses often grew from the olfactory region forward along the nasal turbinate or ventrally along the lateral wall, indiscrete aggregates of tumor cells were also seen intermixed with other tumors or displacing Bowman's glands. The occasional apposition of two distinct tumor types, such as a neuroepithelial tumor and a rhabdomyosarcoma, suggests that the term "collision tumor" might be used in this case, as in the human nomenclature. Since most tumors seemed to be intimate mixtures of the two types and not colliding tumors, perhaps the term "malignant mixed tumor" would be more appropriate.

Table 6. Chemicals not administered by the inhalation route, inducing nasal rhabdomyomas and rhabdomyosarcomas in rats.

Chemical	Species affected	Route
2,6-Xylidine	F344 rats	Dietary
Dimethylvinyl chloride	F344 rats	Oral gavage
1,4-Dioxane	Osborne-Mendel rats	Water
Safrole/corn oil	Osborne-Mendel rats	Oral gavage
Nitrosaminoketone (NNK)	F344 rats	Intraperitoneal

Very bizarre sarcomatous tumors composed of plump spindle cells with large, rounded vesicular nuclei were also observed. These neoplasms formed decussating bundles or appeared as solid sheets with occasional spindle bundles. Multinucleate cells and occasional bizarre mitotic figures were also seen, and large areas often had somewhat of an epithelioid appearance. These tumors were poorly differentiated rhabdomyosarcomas, in my opinion, although a range of diagnoses has been used to define them, including carcinosarcoma and poorly-differentiated carcinoma. Immunohistochemical and electron microscopic studies remain to be done to further characterize such neoplasms.

The most prolific vascular tumor-producing chemical that has been tested by NTP is propylene oxide. A few tumors of the respiratory epithelium were also produced by this chemical in both rats and mice, but the vast majority of lesions observed were vascular in origin and occurred in mice only. The distribution of lesions was usually in the respiratory region, with frequent lesions occurring on the nasal and maxillary turbinates or on the mid- to upper nasal septum. Symmetric lesions were not uncommon, and often diffuse vascular ectasia was also seen. Hemangiomas were usually cavernous with flattened normal-appearing epithelium but with displacement of the normal architecture of the nose at the sites of origin. Thrombosis was evident in some lesions, occasionally organizing into fibrous connective tissue. The possibility of propagating thrombotic lesions, progressively organizing into tumorlike masses instead of actual neoplasms, was considered in this review. Lytic lesions extending into the nasal and maxillary bone were also seen however. These lesions were characterized by vascular channels lined by cells having plump vesicular or pleomorphic nuclei, sometimes multilayered, and rarely with mitotic figures evident. These features were accompanied by a marked periosteal cellular proliferation and by ectasia and thrombosis of vessels away from the central mass into the adjacent narrow cavity or into adjacent vascular beds, such as the periodontal ligament. Destructive tumors with the nuclear features previously described were diagnosed as hemangiosarcomas (Plate 16), but although local invasion appeared to be present, distant metastasis was not reported.

As previously mentioned, a variety of other mesenchymal tumors, which apparently are spontaneous and not induced tumors, were seen in the NTP Archive database. These tumors are listed in Table 1, and some are illustrated in the accompanying figures (Plate 17). Examples of some of these tumors were found in the studies

Table 7. Chemicals in the NTP Archives inducing vascular tumors in the nose of mice.

Chemical	Species affected	Route
Propylene oxide	B6C3F$_1$ mice	Inhalation
1,2-Dibromo-3-chloropropane	B6C3F$_1$ mice	Inhalation

reviewed, whereas others were not or require confirmation by electron microscopy and immunohistochemistry.

Tumors of the Nasolacrimal Duct

Tumors of the nasolacrimal duct were also observed occasionally in the NTP Archive material, usually in association with the administration of a chemical that resulted in tumors of the olfactory or respiratory epithelium. Squamous cell papillomas and carcinomas (Plate 18*A,B*) both occurred primarily in the upper 1/3 of the duct, and frequently near the origin of the duct at the medial canthus of the eye. It should also be noted that the duct bends sharply near the canthus, resulting in a tendency for tangential sectioning that can mimic a squamous cell papilloma.

Tumors of Uncertain Origin

Several examples of a tumor having a distinct morphology but an uncertain origin were observed in the NIP database. To illustrate both the uncertainty and the distinctiveness of the lesions, these tumors were termed "poorly-differentiated spindle-cell tumors of dental or nasolacrimal duct origin." Such tumors occur anterior to the root of the incisor teeth at the level where the nasolacrimal duct lies immediately lateral to the tooth (Plate 19*A,B*). The neoplasm appears to be centered around the tooth but involves the nasolacrimal duct extensively. Typically, the ductal epithelium is characterized by papillary folding of squamous epithelium that is six to eight cell layers thick. Mitotic activity is quite high in the lower 1/3 of the epithelium, and there is a variable degree of subacute inflammation and inflammatory exudate associated with the epithelium. Beneath the epithelium and around the tooth is a population of spindle cells that appeared to be fairly uniform in a given tumor but somewhat pleomorphic when comparing different tumors. Nuclei varied from being elongate and hyperchromatic, to being more vesicular and rounded with a marginated chromatin pattern and a prominent nucleolus. Cellular morphology was either elliptical, indistinct and tightly compacted, or more loosely arranged as polygonal, individual cells with more abundant eosinophilic cytoplasm. Both types often appeared to merge with the adjacent nasolacrimal duct epithelium to a variable ex tent (Plate 19*B*). The pattern of growth was basically in sheets that had no distinctive features. The involved incisor tooth was distorted.

Potentially Preneoplastic Changes

A variety of hyperplastic and other morphologic changes were observed that appeared to correlate with the concurrent development of tumors in the upper respiratory system. In the respiratory epithelium, squamous metaplasia is commonly seen as a result of prolonged irritation, but it was notably extensive following exposure to some carcinogens producing squamous cell neoplasms. Such metaplasia often extended over large portions of the surface area of the nasal cavity and was accompanied by extensive keratin formation (keratin plugging), focal dysplasia of the squamous epithelium, and squamoid basal cell hyperplasia. Small areas of basal cell hyperplasia, either exophytic or endophytic, were also seen in association with papillary or pseudoglandular adenomas or carcinomas of the respiratory epithelium. In the olfactory region, hyperplasia of the olfactory epithelium was either of an undifferentiated basal cell type or of an epidermoid or squamoid type that appeared to have different implications as to the rate and type of progression that followed. In the case of the former appearance, invasive malignant tumors of the epithelium seemed to emerge, whereas the latter seemed to be associated with more local, slower growing inverted papillomas. Hyperplasia of Bowman's glands with cytoplasmic basophilia and large hyperchromatic atypical nuclei were always associated with neoplastic transformation. Other mucosal glands occasionally had similar features and a tendency for clumped or nodular growth, but a progression to tumors was rarely seen.

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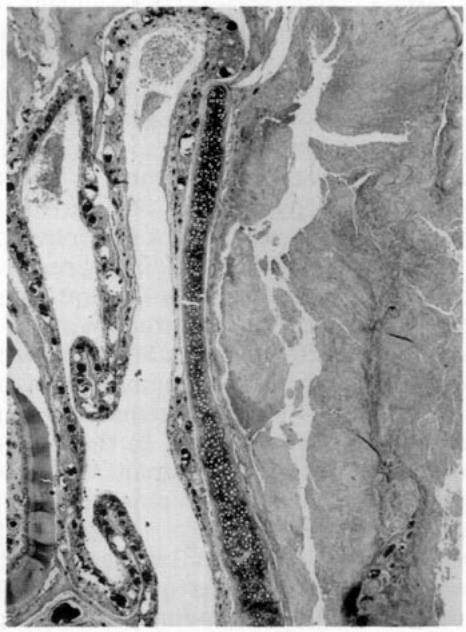


PLATE 1. Diffuse type squamous cell carcinoma induced by 1,4-dioxane administered to rats in drinking water. This tumor obscured the nasal and maxillary turbinates by uniformly and unilaterally replacing the respiratory epithelium of the nasal cavity with a scalloped, parakeratotic squamous epithelium.

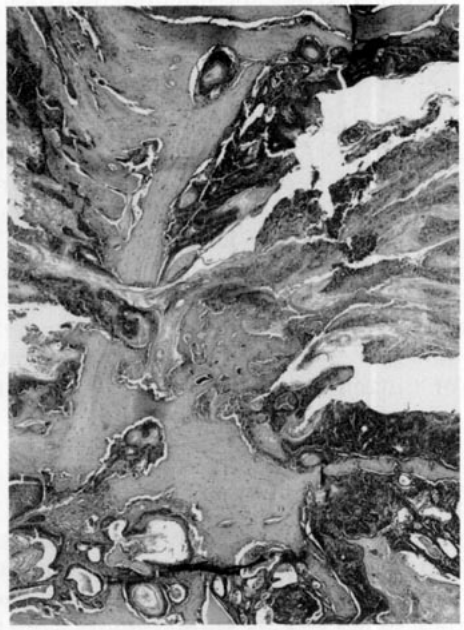
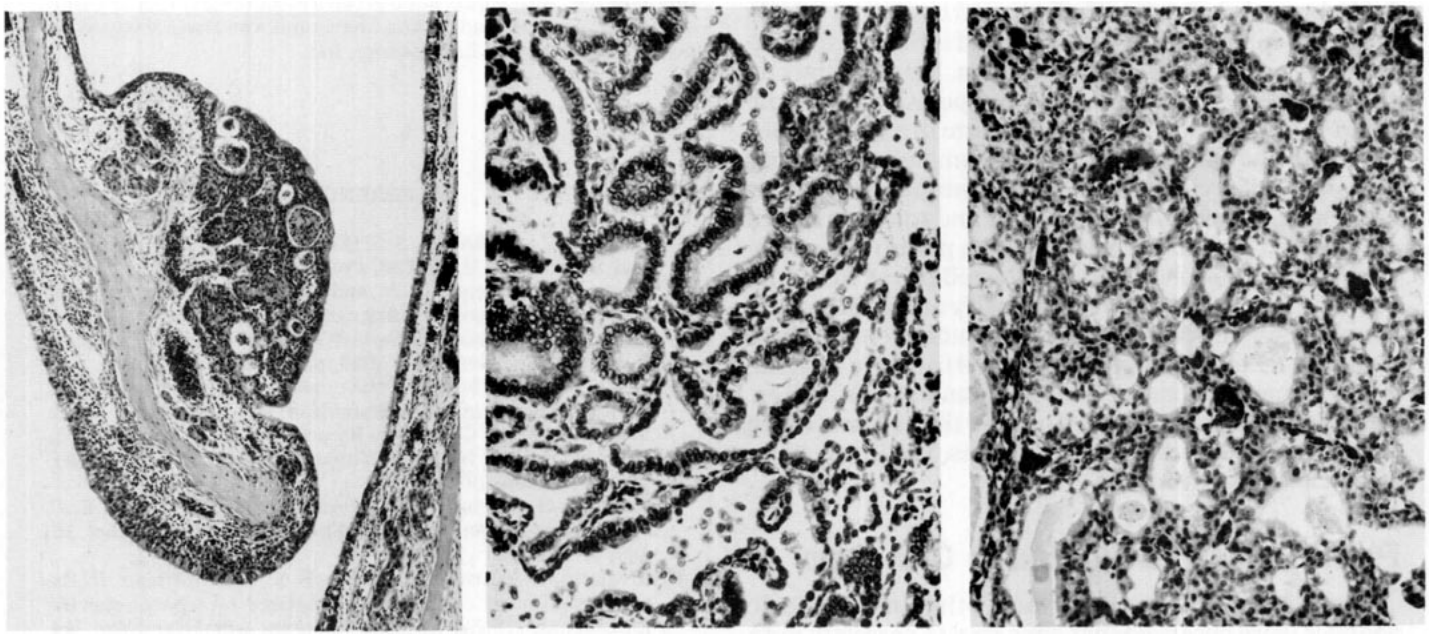
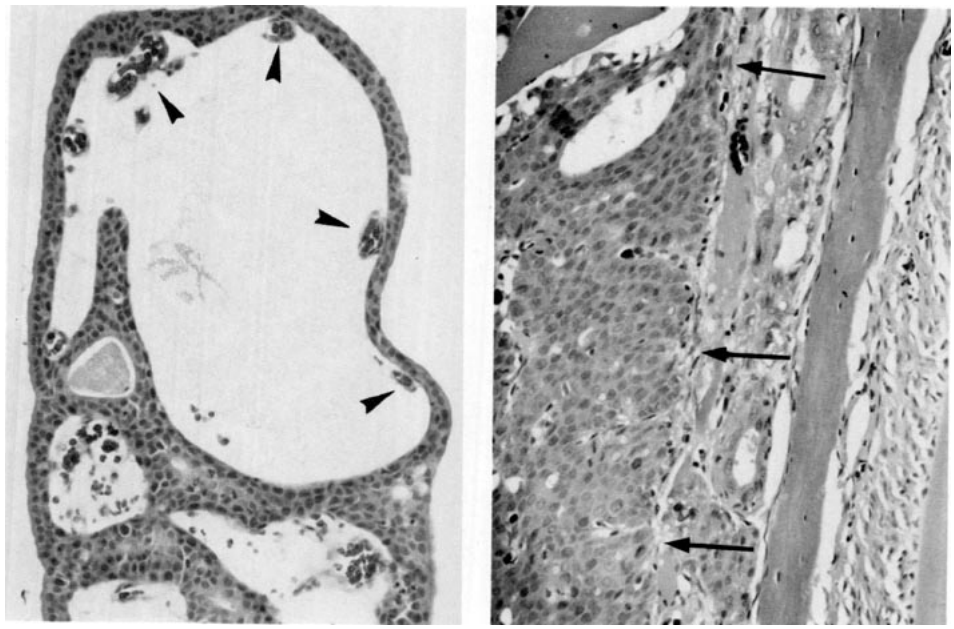


PLATE 2. Adenosquamous carcinoma induced by 2,3-dibromo-1-propanol administered to rats by skin painting. Features of both mucous glands and squamous cell carcinoma were observed.



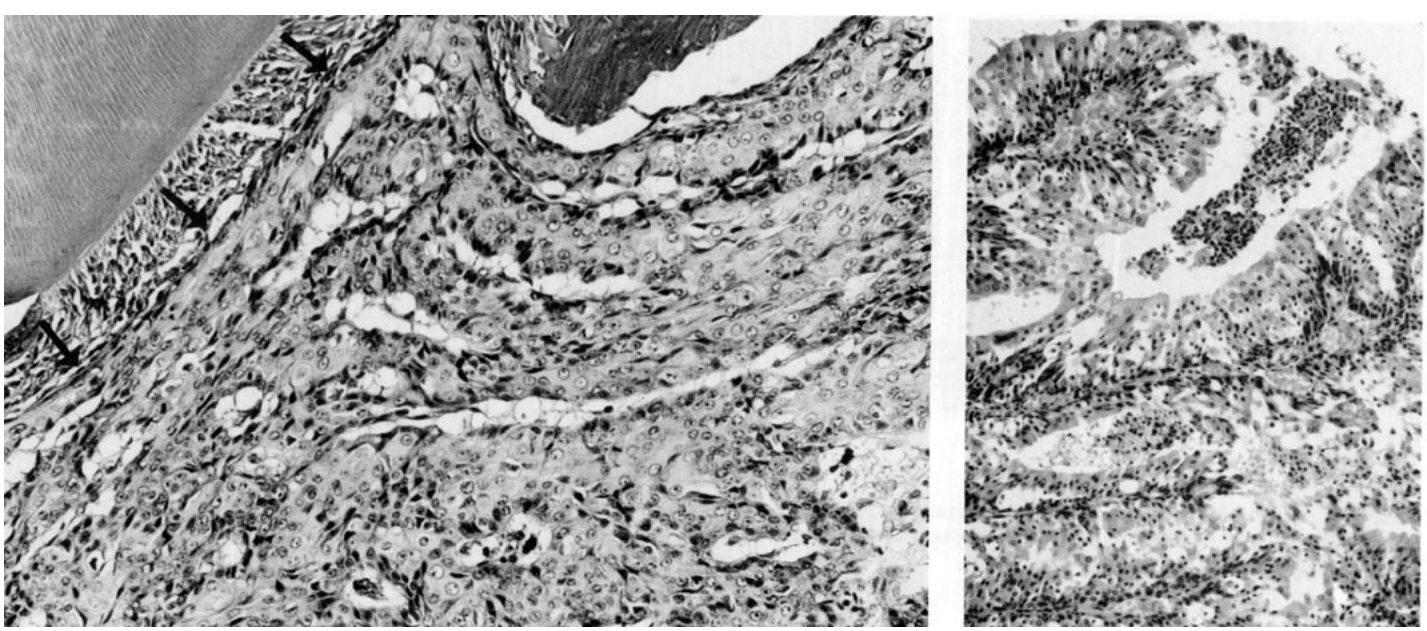
A *B* *C*

PLATE 3. (*A*,*B*) Papillary or pseudoglandular adenomas of the respiratory epithelium. This type of tumor was produced by several chemicals administered by a variety of routes. It was the most common nonsquamous tumor seen in inhalation studies. (*C*) Pseudoglandular adenoma with stratification of nuclei and proliferating and confluent growth of basallike hyperchromatic cells, suggesting progression to a more malignant phenotype.



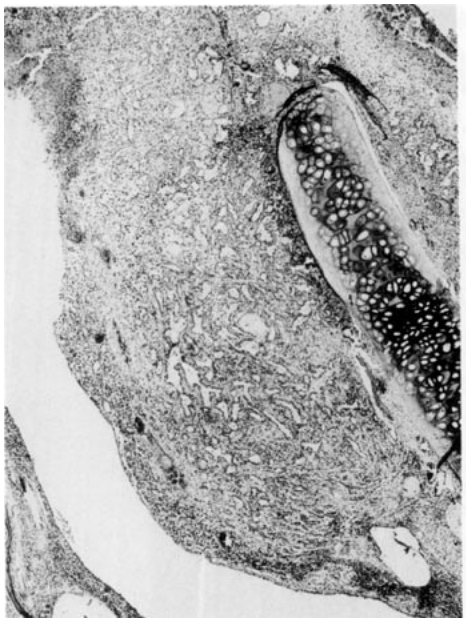
A *B*

PLATE 4. (*A,B*) Epidermoid or transitional adenoma arising along the lateral wall. Features of transitional or stratified cuboidal epithelilum with perivascular edema lakes are pictured (arrow heads indicate vessels within edematous spaces). There was no invasion of the lateral wall basement membrane (arrows).

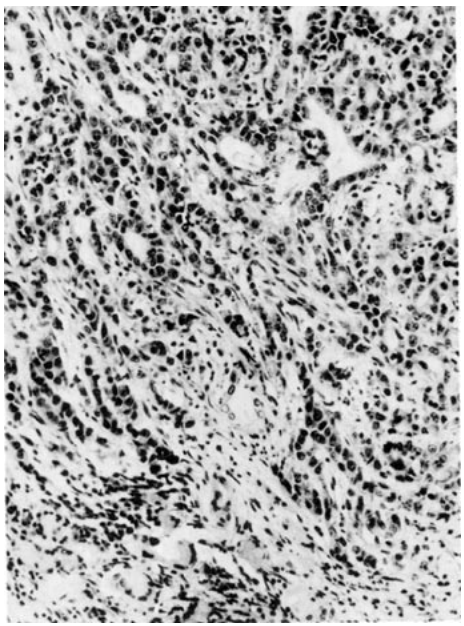


A *B*

PLATE 5. (*A,B*) Epidermoid carcinoma invading through the lateral wall and surrounding the periodontal ligament of the incisor tooth (arrows). These tumors had features of papillary respiratory epithelium with transition zones of stratified cuboidal and "cylindric cells" progressing into a squamoid pattern.



A



B

PLATE 6. Mucosal gland carcinoma with ductular differentiation, arising along the nasal septum. The tumor penetrated through the nasal septum near the vomeronasal organ.

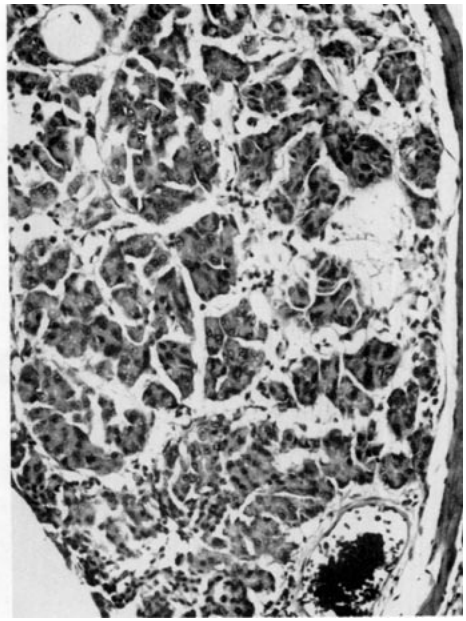
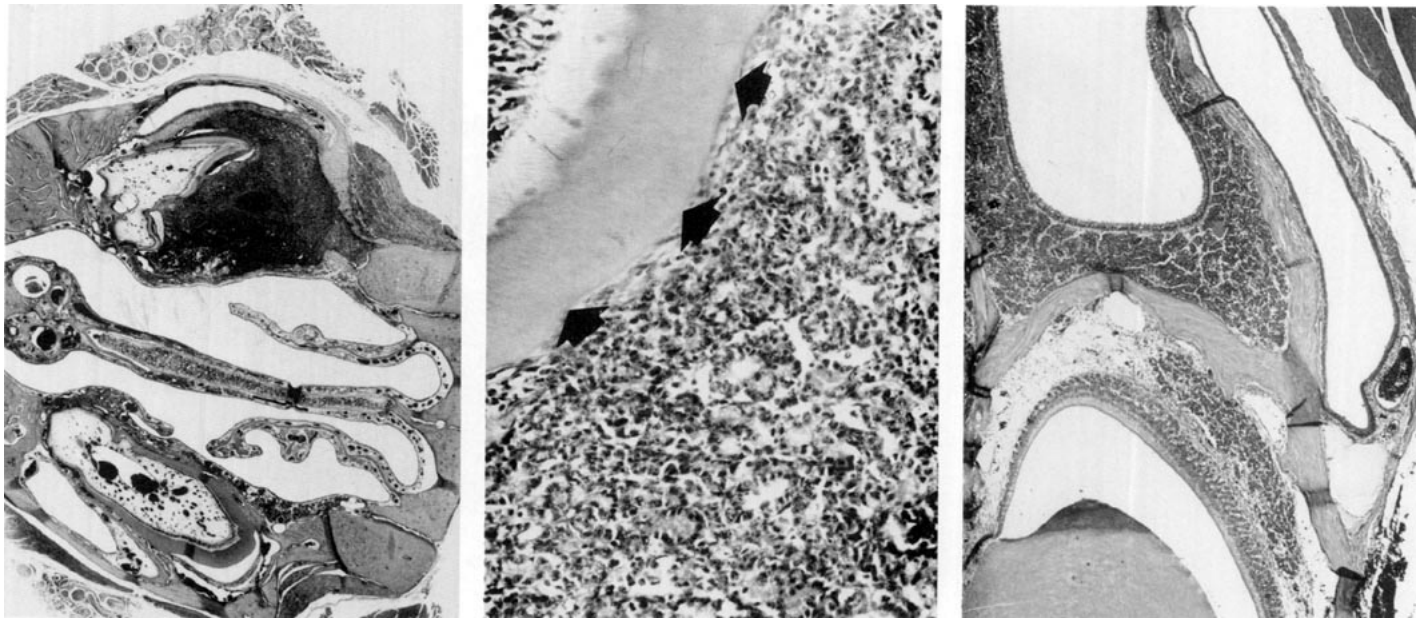


PLATE 7. Mucosal gland adenoma with serous acinar features. The tumor had a compressive growth pattern, growth in irregular cords and some anisonucleosis with a low mitotic rate.



A *B* *C*

PLATE 8. (*A,B,C*) Tumors of the glands of the maxillary sinus with apparent invasion of the periodontal ligament. Tumor cells were slightly smaller with more hyperchromatic nuclei than normal maxillary glandular epithelium. There was also a much higher mitotic rate within the tumor as compared to normal epithelium. (*B*) shows tumor cells abutting the dentine of the tooth (arrows).

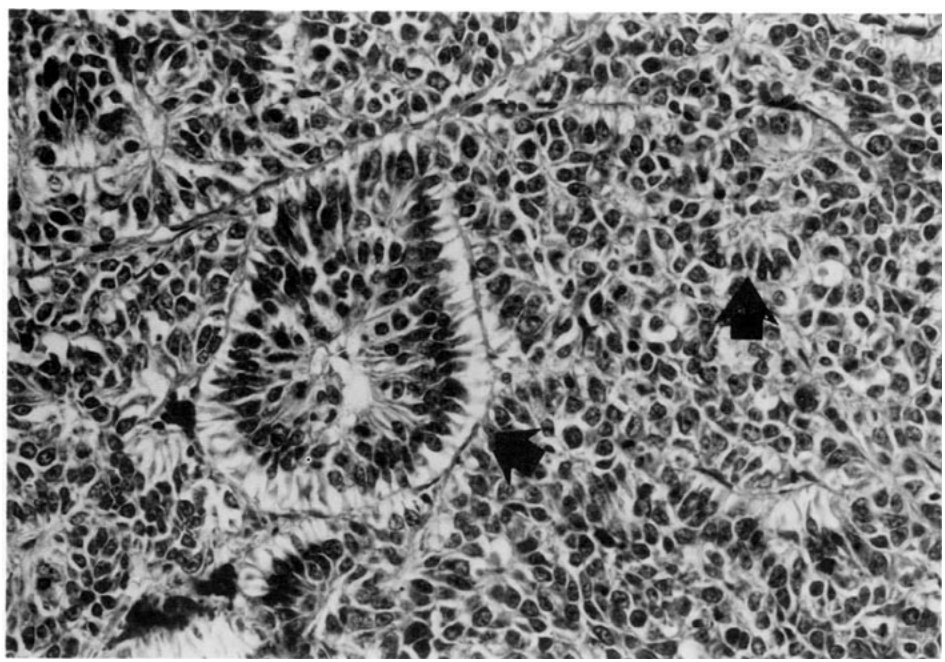
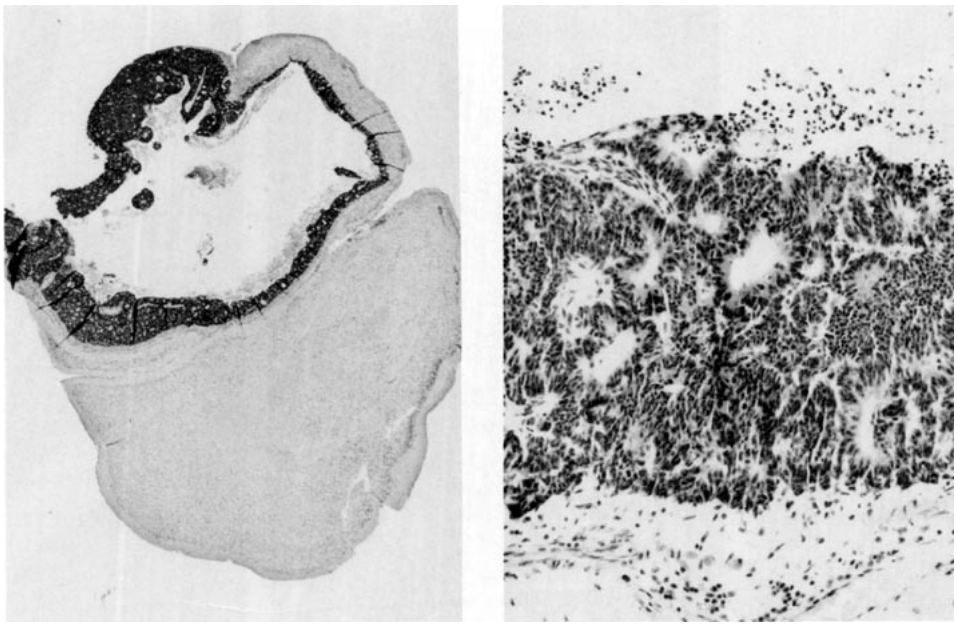


PLATE 9. Neuroepithelial carcinoma arising within the olfactory epithelium with sustentacular cell differentiation. Characteristic features of sustentacular cells include apically or centrally oriented nuclei and cytoplasmic processes (with or without vacuolization) that border blood vessels, and/or form Homer Wright (arrows) or Flexner-Wintersteiner rosettes.



A *B*

PLATE 10. (*A,B*) Neuroepithelial carcinoma with basal cell or neuroblastoma-like (Flexner) rosettes invading from the olfactory region through the cribiform plate into the brain. Tumors of this type were produced by IP injections of F344 rats with procarbazine. The nasal cavity was not originally examined in this study and the origin of these tumors was determined in a retrospective examination.

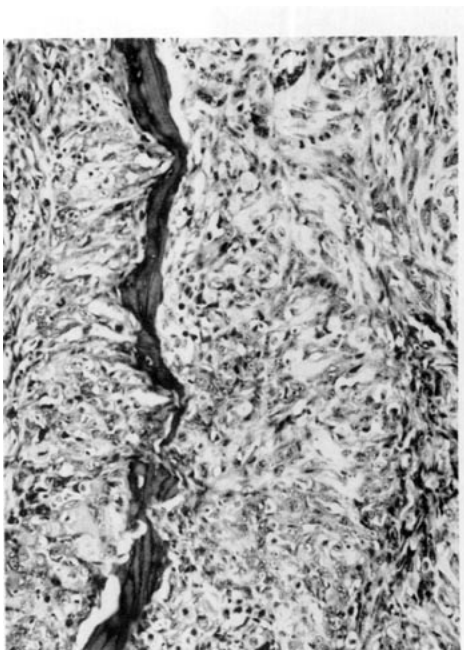


PLATE 11. Anaplastic tumor with epithelial and mesenchymal features arising within the olfactory region. These tumors have been diagnosed as poorly differentiated carcinomas, carcinosarcomas and undifferentiated sarcomas. In this review, most appeared to be poorly differentiated sarcomas or rhabdomyosarcomas.

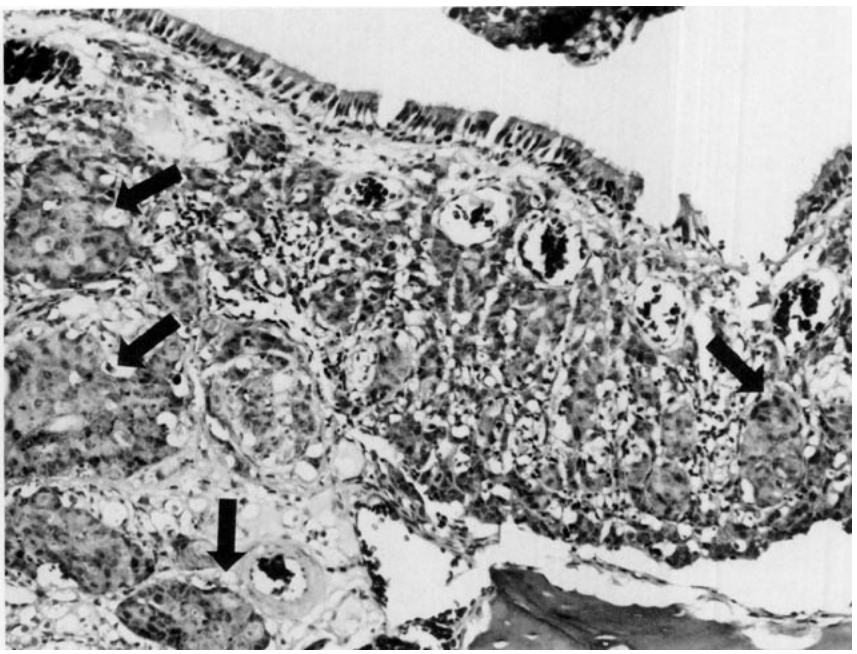


PLATE 12. Early Bowman's gland carcinoma. The aggregation and invasion of Bowman's gland carcinomas (arrows) occurs against a background of diffuse Bowman's gland hyperplasia, necrosis, and atypia.

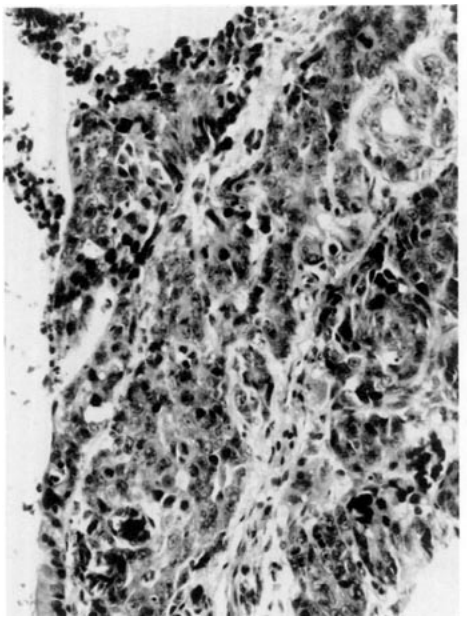


PLATE 13. Advanced Bowman's gland carcinoma. The origin of the tumor is difficult to ascertain at this point but the subepithelial growth pattern, occasional gland formation and the characteristic large nuclei with a prominent nucleoli suggests origin from Bowman's gland.

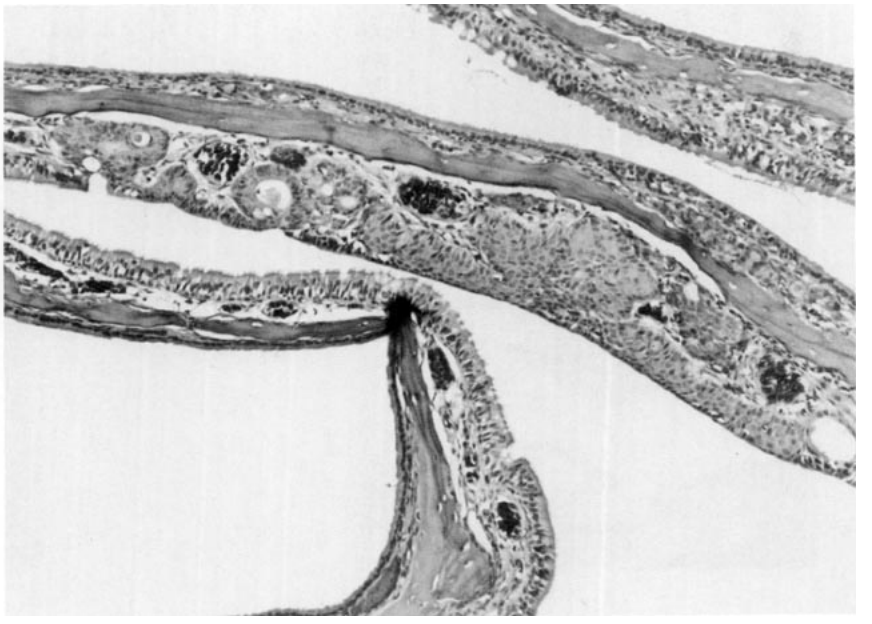


PLATE 14. Epidermoid, squamoid or inverted papillomas in the olfactory region of the nose. These downgrowths of epithelium were characterized by well-circumscribed extensions of "squamoid" epithelium into the lamina propria with little if any indication of progression. Nuclei characteristically did not flatten and orient parallel to the basement membrane as in true squamous epithelium.

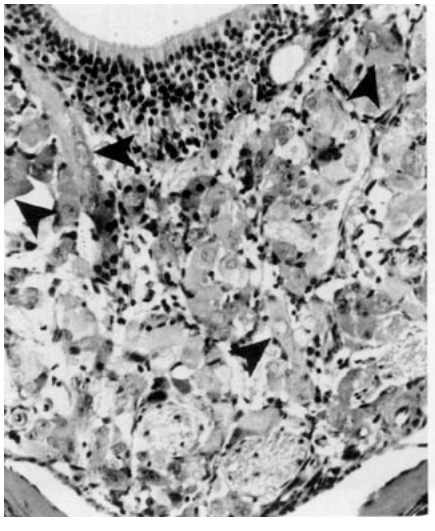


PLATE 15. Rhabdomyoblasts (arrowheads) in the lamina propria of the olfactory region of the nose from a rat exposed to NNK or 2,6-xylidine. Large syncytial cells with abundant eosinophilic fibrillar cytoplasm are usually also seen with these single nucleated cells when multiple sections are taken. Striations can be demonstrated with little difficulty with standard H&E staining. Characteristic striated muscle filament banding has been demonstrated by transmission electron microscopy.

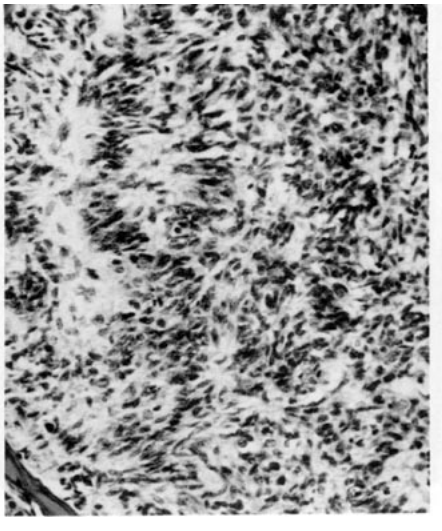


PLATE 16. Hemangiosarcoma invading into the nasal and maxillary bone from a mouse exposed to propylene oxide via the inhalation route. The tumor was characterized by large vesicular nuclei with some layering, lining irregular vascular spaces. A marked periosteal reactive response was also observed in the affected bone.

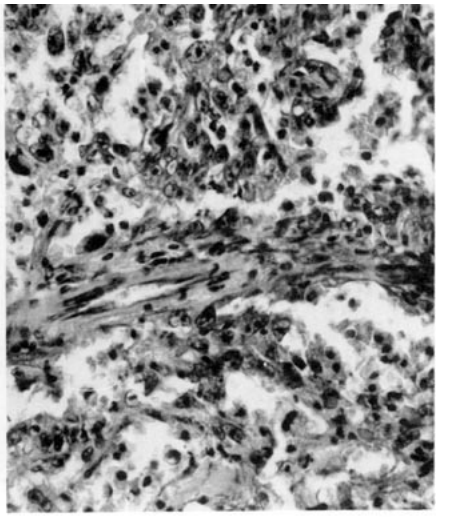
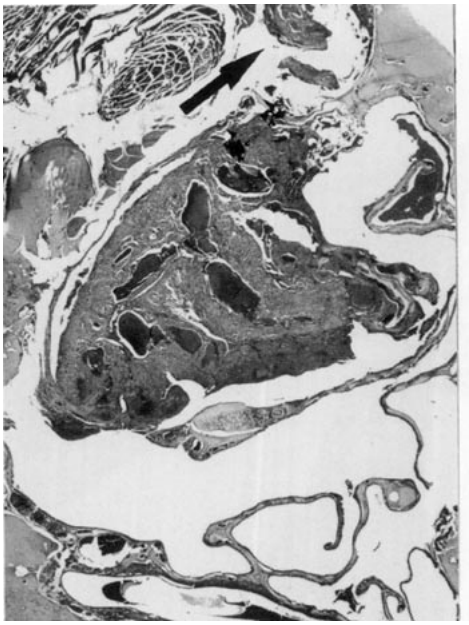
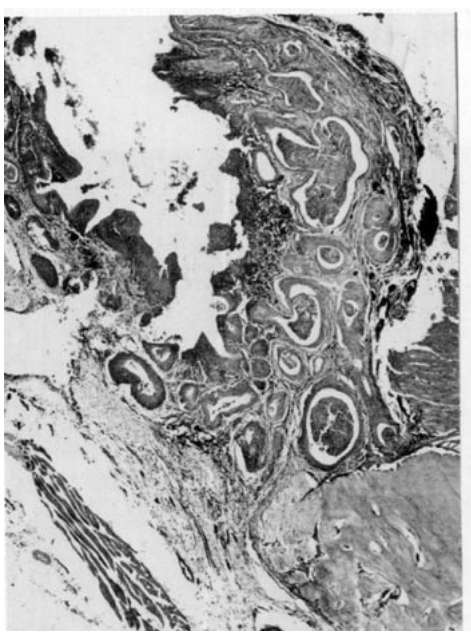


PLATE 17. Malignant Schwannoma along the nasal septum of a mouse. The tumor extensively involved the soft tissue surrounding the nasal cavity and the exact origin of the tumor, whether intra- or extranasal was uncertain.

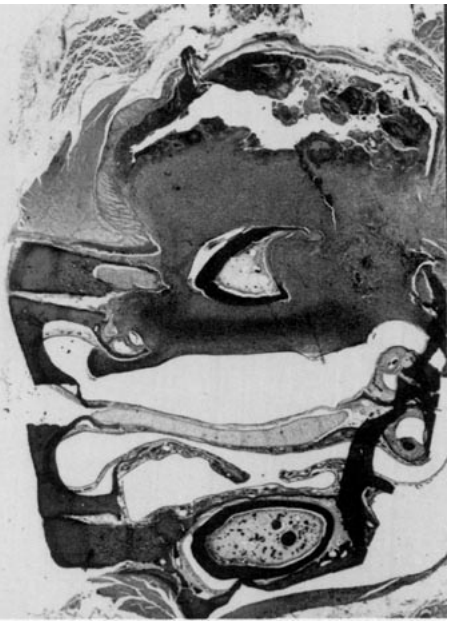


A

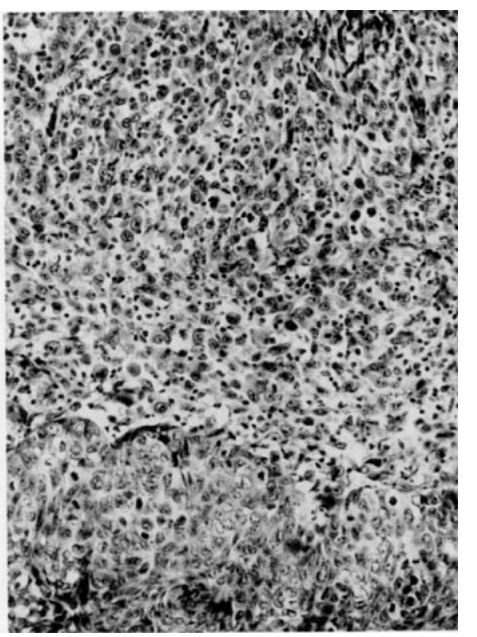


B

PLATE 18. (*A,B*) Squamous cell carcinoma (arrow) arising within the nasolacrimal duct of a rat with a concurrent olfactory epithelial carcinoma. The olfactory tumor was diagnosed originally while the nasolacrimal tumor was overlooked. (*B*) High magnification of squamous cell carcinoma indicated in (*A*) by arrows.



A



B

PLATE 19. (*A,B*) Spindle cell tumor of either nasolacrimal duct or dental origin. This tumor was characterized by small spindle or fusiform epithelioid cells centering around the incisor tooth root and abutting the nasolacrimal duct epithelium which was inflamed and proliferating in papillary folds. The origin of the tumor was controversial.